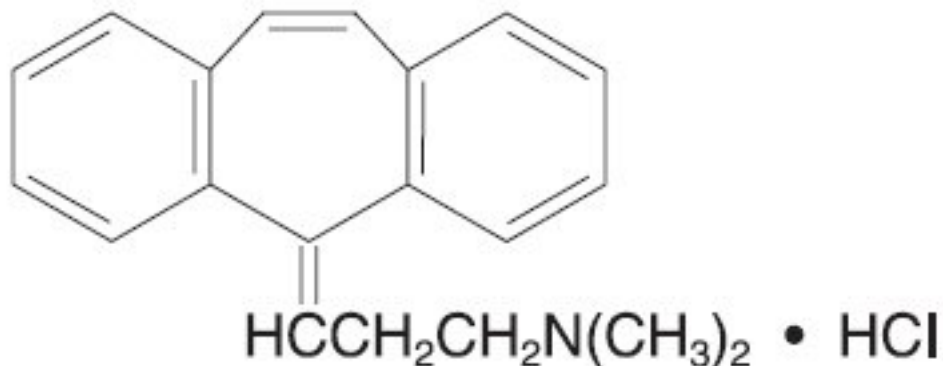


FLEXERIL - cyclobenzaprine hydrochloride tablet, film coated
Keltman Pharmaceuticals Inc

DESCRIPTION

Cyclobenzaprine hydrochloride is a white, crystalline tricyclic amine salt with the empirical formula $C_{20}H_{21}N \cdot HCl$ and a molecular weight of 311.9. It has a melting point of 217°C, and a pK_a of 8.47 at 25°C. It is freely soluble in water and alcohol, sparingly soluble in isopropanol, and insoluble in hydrocarbon solvents. If aqueous solutions are made alkaline, the free base separates.

Cyclobenzaprine HCl is designated chemically as 3-(5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)-*N,N*-dimethyl-1-propanamine hydrochloride, and has the following structural formula:



Each tablet for oral administration contains 10 mg Cyclobenzaprine Hydrochloride, USP.

Each tablet contains the following inactive ingredients: anhydrous lactose, carnauba wax, corn starch, croscopovidone, hypromellose, magnesium stearate, pregelatinized starch, polyethylene glycol, polysorbate 80, titanium dioxide, D&C yellow #10, FD&C Blue #2, & FD&C yellow #6.

CLINICAL PHARMACOLOGY

Cyclobenzaprine HCl relieves skeletal muscle spasm of local origin without interfering with muscle function. It is ineffective in muscle spasm due to central nervous system disease.

Cyclobenzaprine reduced or abolished skeletal muscle hyperactivity in several animal models. Animal studies indicate that cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle. Such studies show that cyclobenzaprine acts primarily within the central nervous system at brain stem as opposed to spinal cord levels, although its action on the latter may contribute to its overall skeletal muscle relaxant activity. Evidence suggests that the net effect of cyclobenzaprine is a reduction of tonic somatic motor activity, influencing both gamma (γ) and alpha (α) motor systems.

Pharmacological studies in animals showed a similarity between the effects of cyclobenzaprine and the structurally related tricyclic antidepressants, including reserpine antagonism, norepinephrine potentiation, potent peripheral and central anticholinergic effects, and sedation. Cyclobenzaprine caused slight to moderate increase in heart rate in animals.

Cyclobenzaprine is well absorbed after oral administration, but there is a large intersubject variation in plasma levels. Cyclobenzaprine is eliminated quite slowly with a half-life as long as one to three days. It is highly bound to plasma protein, is extensively metabolized primarily to glucuronide-like conjugates, and is excreted primarily via the kidneys.

No significant effect on plasma levels or bioavailability of cyclobenzaprine hydrochloride or aspirin was noted when single or multiple doses of the two drugs were administered concomitantly. Concomitant administration of cyclobenzaprine hydrochloride and aspirin is usually well tolerated and no unexpected or serious clinical or laboratory adverse effects have been observed. No studies have been performed to indicate whether cyclobenzaprine enhances the clinical effect of aspirin or other analgesics, or whether analgesics enhance the clinical effect of cyclobenzaprine in acute musculoskeletal conditions.

Clinical Studies

Controlled clinical studies show that cyclobenzaprine hydrochloride significantly improves the signs and symptoms of skeletal muscle spasm as compared with placebo. The clinical responses include improvement in muscle spasm as determined by palpation, reduction in local pain and tenderness, increased range of motion, and less restriction in activities of daily living. When daily observations were made, clinical improvement was observed as early as the first day of therapy.

Eight double-blind controlled clinical studies were performed in 642 patients comparing cyclobenzaprine hydrochloride, diazepam, and placebo. Muscle spasm, local pain and tenderness, limitation of motion, and restriction in activities of daily living were evaluated. In three of these studies there was a significantly greater improvement with cyclobenzaprine than with diazepam, while in the other studies the improvement following both treatments was comparable.

Although the frequency and severity of adverse reactions observed in patients treated with cyclobenzaprine were comparable to those observed in patients treated with diazepam, dry mouth was observed more frequently in patients treated with cyclobenzaprine and dizziness more frequently in those treated with diazepam. The incidence of drowsiness, the most frequent adverse reaction, was similar with both drugs.

Analysis of the data from controlled studies shows that cyclobenzaprine produces clinical improvement whether or not sedation occurs.

Surveillance Program

A post-marketing surveillance program was carried out in 7607 patients with acute musculoskeletal disorders, and included 297 patients treated for 30 days or longer. The overall effectiveness of cyclobenzaprine was similar to that observed in the double-blind controlled studies; the overall incidence of adverse effects was less (see ADVERSE REACTIONS).

INDICATIONS AND USAGE

Cyclobenzaprine hydrochloride tablets are indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions.

Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, limitation of motion, and restriction in activities of daily living.

Cyclobenzaprine hydrochloride tablets should be used only for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.

Cyclobenzaprine HCL has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease, or in children with cerebral palsy.

CONTRAINDICATIONS

Hypersensitivity to the drug.

Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation.

Acute recovery phase of myocardial infarction, and patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure.

Hyperthyroidism.

WARNINGS

Cyclobenzaprine is closely related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. In short term studies for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm, some of the more serious central nervous system reactions noted with the tricyclic antidepressants have occurred (see WARNINGS, below, and ADVERSE REACTIONS).

Cyclobenzaprine may interact with monoamine oxidase(MAO)inhibitors.hyperpyretic crisis,severe convulsions and deaths have occurred in patients receiving tricyclic antidepressants and MAO inhibitor drugs.

Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke.

Cyclobenzaprine may enhance the effects of alcohol, barbiturates, and other CNS depressants.

PRECAUTIONS

General

Because of its atropine-like action, cyclobenzaprine hydrochloride should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

Information for Patients

Cyclobenzaprine may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Drug Interactions

Cyclobenzaprine may enhance the effects of alcohol, barbiturates, and other CNS depressants.

Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In rats treated with cyclobenzaprine hydrochloride for up to 67 weeks at doses of approximately 5 to 40 times the maximum recommended human dose, pale, sometimes enlarged, livers were noted and there was a dose-related hepatocyte vacuolation with lipidosis. In the higher dose groups this microscopic change was seen after 26 weeks and even earlier in rats which died prior to 26 weeks; at lower doses, the change was not seen until after 26 weeks.

Cyclobenzaprine did not affect the onset, incidence or distribution of neoplasia in an 81-week study in the mouse or in a 105-week study in the rat.

At oral doses of up to 10 times the human dose, cyclobenzaprine did not adversely affect the reproductive performance or fertility of male or female rats. Cyclobenzaprine did not demonstrate mutagenic activity in the male mouse at dose levels of up to 20 times the human dose.

Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in rats, mice and rabbits at doses up to 20 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus due to cyclobenzaprine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because cyclobenzaprine hydrochloride is closely related to the tricyclic antidepressants, some of which are known to be excreted in human milk, caution should be exercised when cyclobenzaprine hydrochloride is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of cyclobenzaprine hydrochloride in children below 15 years of age have not been established.

ADVERSE REACTIONS

The following list of adverse reactions is based on the experience in 473 patients treated with cyclobenzaprine hydrochloride controlled clinical studies, 7607 patients in the post-marketing surveillance program, and reports received since the drug was marketed. The overall incidence of adverse reactions among patients in the surveillance program was less than the incidence in the controlled clinical studies.

The adverse reactions reported most frequently with cyclobenzaprine hydrochloride were drowsiness, dry mouth and dizziness. The incidence of these common adverse reactions was lower in the surveillance program than in the controlled clinical studies:

	Clinical Studies	Surveillance Program
Drowsiness	39%	16%
Dry Mouth	27%	7%
Dizziness	11%	3%

Among the less frequent adverse reactions, there was no appreciable difference in incidence in controlled clinical studies or in the surveillance program. Adverse reactions which were reported in 1% to 3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion.

Incidence in less than 1 in 100 The following adverse reactions have been reported in post-marketing experience or with an incidence of less than 1% of patients in clinical trials with the 10 mg tablet:

Body as a Whole: Syncope; malaise.

Cardiovascular: Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension.

Digestive: Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice and cholestasis.

Musculoskeletal: Local weakness.

Nervous System and Psychiatric: Ataxia; vertigo; dysarthria; tremors; hypertonia; convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; psychosis, abnormal thinking and dreaming; hallucinations; excitement; paresthesia;

Skin: Sweating; skin rash; urticaria.

Special Senses: Ageusia; tinnitus.

Urogenital: Urinary frequency and/or retention.

Causal Relationship Unknown

Other reactions, reported rarely for cyclobenzaprine hydrochloride under circumstances where a causal relationship could not be established or reported for other tricyclic drugs, are listed to serve as alerting information to physicians:

Body as a Whole: Chest pain; edema.

Cardiovascular: Hypertension; myocardial infarction; heart block; stroke.

Digestive: Paralytic ileus; tongue discoloration; stomatitis; parotid swelling.

Endocrine: Inappropriate ADH syndrome.

Hematic and Lymphatic: Purpura; bone marrow depression; leukopenia; eosinophilia; thrombocytopenia.

Metabolic, Nutritional and Immune: Elevation and lowering of blood sugar levels; weight gain or loss.

Musculoskeletal: Myalgia.

Nervous System and Psychiatric: Decreased or increased libido; abnormal gait; delusions; peripheral neuropathy; Bell's palsy; alteration in EEG patterns; extrapyramidal symptoms.

Respiratory: Dyspnea.

Skin: Photosensitization; alopecia; pruritus.

Urogenital: Impaired urination; dilatation of urinary tract; impotence; testicular swelling; gynecomastia; breast enlargement; galactorrhea.

DRUG ABUSE AND DEPENDENCE

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when cyclobenzaprine hydrochloride is administered, even though they have not been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration rarely may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE

MANIFESTATIONS

High doses may cause temporary confusion, disturbed concentration, transient visual hallucinations, agitation, hyperactive reflexes, muscle rigidity, vomiting, or hyperpyrexia in addition to anything listed under ADVERSE REACTIONS.

Based on the known pharmacologic actions of the drug, overdose may cause drowsiness, hypothermia, tachycardia and other cardiac rhythm abnormalities such as bundle branch block, ECG evidence of impaired conditions, and congestive heart failure. Other manifestations may be dilated pupils, convulsions, severe hypotension, stupor and coma.

The acute oral LD₅₀ of cyclobenzaprine hydrochloride is approximately 338 and 425 mg/kg in mice and rats, respectively.

TREATMENT

Treatment is symptomatic and supportive. Empty the stomach as quickly as possible by emesis, followed by gastric lavage. After gastric lavage, activated charcoal may be administered. Twenty to 30 g of activated charcoal may be given every four to six hours during the first 24 to 48 hours after ingestion. An ECG should be taken and close monitoring of cardiac function must be instituted if there is any evidence of dysrhythmia. Maintenance of an open airway, adequate fluid intake, and regulation of body temperature are necessary. The intravenous administration of 1-3 mg of physostigmine salicylate is reported to reverse symptoms of poisoning by atropine and other drugs with anticholinergic activity. Physostigmine may be helpful in the treatment of cyclobenzaprine overdose because physostigmine is rapidly metabolized, the dosage of physostigmine should be repeated as required, particularly if life-threatening signs such as arrhythmias, convulsions, and deep coma recur or persist after the initial dosage of physostigmine. Because physostigmine itself may be toxic, it is not recommended for routine use.

Standard medical measures should be used to manage circulatory shock and metabolic acidosis. Cardiac arrhythmias may be treated with neostigmine, pyridostigmine, or propranolol. When signs of cardiac failure occur, the use of short-acting digitalis preparation should be considered. Close monitoring of cardiac function for not less than five days is advisable.

Anticonvulsants may be given to control seizure.

Dialysis is probably of no value because of low concentrations of the drug.

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdosage have occurred with this class of drugs.

DOSAGE AND ADMINISTRATION

The usual dosage of cyclobenzaprine HCL is 10 mg three times a day, with the range of 20-40 mg a day in divided doses. Dosage should not exceed 60 mg a day. Use of cyclobenzaprine for periods longer than two or three weeks is not recommended (see INDICATIONS AND USAGE).

HOW SUPPLIED

Cyclobenzaprine Hydrochloride Tablets, USP 10 mg round, yellow, Round, unscored, filmcoated tablets in bottles of 10, 15, 45. debossed: PLIVA 563

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]

Dispense in well closed container

Manufactured by:

Pliva®, Inc Pomona, NY 10970

Manufactured for:

Keltman Pharmaceuticals Inc.

1 Lakeland Square, Suite A

Flowood, Ms 39232

R4

PRINCIPAL DISPLAY PANEL

NDC 68387-500-10

Cyclobenzaprine HCL 10 mg;

Generic flexeril 10mg

10 tablets

Each tablet contain 10 mg cyclobenzaprine HCL

Rx only

Keltman Pharmaceuticals, Inc.

NDC: 68387-500-10
Cyclobenzaprine HCL 10mg
 Generic Flexeril 10mg
10 Tablets
 Each tablet contains 10mg cyclobenzaprine HCL

Rx Only

Lot: 311521 1 Exp: 11/2011 Rx #: 41568
 Store at controlled room temperature 20-25 C (68-77 F).
 Keep out of reach of children. Dosage: See package insert
 Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom prescribed.

Manufactured by: Pliva, Inc. Pomona, NY 10970
 Distributed by: Keltman Pharmaceuticals, Inc. Flowood, MS 39232
 Call your doctor for medical advice about side effects.
 You may report side effects to FDA at 1-800-FDA-1088.

68387-0500-10++3115211

Take ___ tablet(s) ___ time(s) daily or
 every ___ hours for ___ days.

NDC: 68387-500-10 Rx #: 41568
 Generic Flexeril 10mg
 (cyclobenzaprine HCL)
 Lot: 311521 1 Exp: 11/2011 Chart

NDC: 68387-500-10 Rx #: 41568
 Generic Flexeril 10mg
 (cyclobenzaprine HCL)
 Lot: 311521 1 Exp: 11/2011 Patient

NDC: 68387-500-10 Rx #: 41568
 Generic Flexeril 10mg
 (cyclobenzaprine HCL)
 Lot: 311521 1 Exp: 11/2011 Bill

NDC: 68387-500-10 Rx #: 41568
 Generic Flexeril 10mg
 (cyclobenzaprine HCL)
 Lot: 311521 1 Exp: 11/2011 Log

PRINCIPAL DISPLAY PANEL

NDC 68387-500-15

Cyclobenzaprine HCL 10 mg;

Generic flexeril 10mg

15 tablets

Each tablet contain 10 mg cyclobenzaprine HCL

Rx only

Keltman Pharmaceuticals, Inc.

NDC: 68387-500-15
Cyclobenzaprine HCL 10mg
 Generic Flexeril 10mg
15 Tablets
 Each tablet contains 10mg cyclobenzaprine HCL

Rx Only

Lot: 307319 1 Exp: 2/2011 Rx #: 4174
 Store at controlled room temperature 20-25 C (68-77 F).
 Keep out of reach children. Dosage: See package insert.
 Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom prescribed.

Manufactured by: Pliva, Inc. Pomona, NY 10970
 Distributed by: Keltman Pharmaceuticals, Inc. Flowood, MS 39232

68387-0500-15++3073191

Take ___ tablet(s) ___ time(s)
 daily or every ___ hours for ___ days.

NDC: 68387-500-15 Rx #: 4174
 Generic Flexeril 10mg
 (cyclobenzaprine HCL)
 Lot: 307319 1 Exp: 2/2011 Chart

NDC: 68387-500-15 Rx #: 4174
 Generic Flexeril 10mg
 (cyclobenzaprine HCL)
 Lot: 307319 1 Exp: 2/2011 Patient

NDC: 68387-500-15 Rx #: 4174
 Generic Flexeril 10mg
 (cyclobenzaprine HCL)
 Lot: 307319 1 Exp: 2/2011 Bill

NDC: 68387-500-15 Rx #: 4174
 Generic Flexeril 10mg
 (cyclobenzaprine HCL)
 Lot: 307319 1 Exp: 2/2011 Log

PRINCIPAL DISPLAY PANEL

NDC 68387-500-45

Cyclobenzaprine HCL 10 mg;

Generic flexeril 10mg

45 tablets

Each tablet contain 10 mg cyclobenzaprine HCL

Rx only

Keltman Pharmaceuticals, Inc.

68387-0500-45++38010A1



Take ___ tablet(s) ___ time(s)
daily or every ___ hours for ___
days.

NDC: 68387-500-45 Cyclobenzaprine HCL 10mg

Generic Flexeril 10mg

45 Tablets

Each tablet contains 10mg cyclobenzaprine HCL

Rx Only

Lot: 38010A 1

Exp: 1/2011

Rx #: 184541

Store at controlled room temperature 20-25 C (68-77 F).

Keep out of reach children. Dosage: See package insert
Caution: Federal law prohibits transfer of this drug to any
person other than the patient for whom prescribed.

Manufactured by: Pliva, Inc. Pomona, NY 10970

Distributed by: Keltman Pharmaceuticals, Inc. Flowood, MS 39232

NDC: 68387-500-45 Rx #: 184541
Generic Flexeril 10mg
(cyclobenzaprine HCL)

Lot: 38010A 1 Exp: 1/2011

Chart

NDC: 68387-500-45 Rx #: 184541
Generic Flexeril 10mg
(cyclobenzaprine HCL)

Lot: 38010A 1 Exp: 1/2011

Patient

NDC: 68387-500-45 Rx #: 184541
Generic Flexeril 10mg
(cyclobenzaprine HCL)

Lot: 38010A 1 Exp: 1/2011

Bill

NDC: 68387-500-45 Rx #: 184541
Generic Flexeril 10mg
(cyclobenzaprine HCL)

Lot: 38010A 1 Exp: 1/2011

Log